

**REMARKS**

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

**I. Status of the Claims and Amendments**

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. Because these amendments place the application in better condition for consideration on appeal, entry of the amendments is respectfully requested.

Claim 1 is requested to be amended. The amendments specify that the cell is an “*E. coli* cell” and that the oligosaccharide comprises “lactose.” Support for these amendments can be found throughout the specification as-filed including page 6, line 6 and page 16, lines 15-18. No new matter is being added.

Claim 14 is requested to be canceled without prejudice or disclaimer.

After amending the claims as set forth above, claims 1, 2, 5-24, and 26-46 are pending, and claims 15-17, 21-24, 29, 31-38, and 40-46 are withdrawn. Thus, claims 1, 2, 5-14, 18-20, 26-28, 30, and 39 are pending and subject to examination on the merits.

**II. Claim Objections – 37 C.F.R. § 1.75(c)**

Claim 14 is objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. According to the Office Action, “Claim 14 does not further limit Claim 1 as all of the precursors of Claim 1 ... are carbohydrates.” Office Action at 2.

While not acquiescing in the propriety of the objection, Applicants have canceled claim 14. Thus, the objection is rendered moot.

**III. Claim Rejections – 35 U.S.C. § 112, First Paragraph**

**A. Written Description**

Claims 1, 2, 5-14, 18-20, 26-28, 30 and 39 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description support. According to the Office Action, “merely providing lists of sources of each individual component is insufficient to provide an adequate written description of the methods recited in the claims as each gene cannot be used with each with every precursor in every microorganism for the synthesis of any desired oligosaccharide.” Office Action at 3. Applicants respectfully traverse this ground of rejection.

While not acquiescing in the propriety of the rejection, Applicants have amended claim 1 to specify the type of bacterial cell and oligosaccharide. Specifically, claim 1 has been amended to recite that the cell is an *E. coli* cell. In addition, claim 1 has been amended to recite that the oligosaccharide comprises lactose.

The specification provides a complete description of the presently claimed invention. For example, pages 12-14 of the specification describe how the recited exogenous precursors may be internalized in an *E. coli* cell to practice the claimed method. This description includes the genotype of *E. coli* cells that may be used to prevent enzymatic degradation of the exogenous precursor. *See Spec. at page 14, lines 21-23.* The specification also describes how to prepare specific oligosaccharides. *See Spec. at page 15, line 1 – page 16, line 13.* The specification also states that makes it possible to produce “a large number of oligosaccharides obtained by glycosylation of lactose.” *Spec. at page 16, lines 15-18.* The specification goes on to describe how this glycosylation can be accomplished. The description is supported by actual working examples describing in great detail how the claimed method can be performed. This description goes beyond providing “lists of sources of each individual component” by describing how the components can be used together to perform the claimed method. Accordingly, the specification does not provide mere lists but instead describes in detail how the claimed method can be practiced by the skilled artisan. Thus, the specification provides an adequate written description of the claimed invention.

The Office Action states that “[p]racticing the methods of the claims required detailed knowledge of the biosynthetic pathways for the synthesis of any desired oligosaccharide, knowledge of the source of all enzymes necessary for the synthesis, knowledge of the metabolic/catabolic pathways present in the microorganism to be used and detailed knowledge of how these factors are interrelated such that one obtains the desired result.” Office Action at 4. However, the specification contains extensive guidance to practice the claimed invention, as discussed above. The specification includes a description of the biosynthetic pathways to produce certain oligosaccharides. *See, e.g.*, spec. at page 15, line 1 – page 16, line 13. The description also includes description of the *E. coli* cells that may be used and the enzymes that can be used for synthesis. *See, e.g.*, spec. at pages 12-14. One of skill in the art would readily understand Applicants to be in possession of the claimed invention based on this description and could readily modify the teaches to make a variety of oligosaccharides. Accordingly, the description provided by the specification provides written description support for the presently claimed invention.

Even if the examiner persists in rejecting the claims as allegedly lacking written description support, the rejection should be withdrawn as to at least claim 7. Claim 7 specifies that the enzyme of claim 1 is one of a recited list of glycosyl-transferases. The specification describes how these specific glycosyl-transferases can be used with *E. coli* cells to produce oligosaccharides, as presently recited. For example, the working examples describe the use of some the recited glycosyl-transferases,  $\alpha$ -2,3-sialyl transferase,  $\alpha$ -1, 3-fucosyl-transferase,  $\beta$ -1, 3-N-acetyl-galactosaminyl-transferase, and  $\beta$ -1,4-galactosyl-transferase (page 25, ll. 11-12 and 24; page 32, line 20-21; page 33, line 19-20). This description provides far more than “lists of sources of each individual component,” because it shows how to actually use the components together. Thus, at least claim 7 has written description support.

## **B. Enablement**

Claims 1-14, 18-20, 25-28, 30, and 30 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. According to the Office Action, the specification “does not reasonably provide enablement for methods of making any oligosaccharide from

lactose, sialic acid, an  $\alpha$ -galactoside, or a  $\beta$ -galactoside in any bacterium.” Office Action at 5-6. Applicants respectfully traverse this ground of rejection.

While not acquiescing in the propriety of the rejection, Applicants have amended the claims such that they are no longer directed to “any oligosaccharide” in “any bacterium.” Instead, the claims recite that the oligosaccharide comprises lactose and that the bacterial cell is an *E. coli* cell. As discussed below, the specification allows one of skill in the art to practice the claimed invention without undue experimentation.

The specification provides sufficient guidance to allow a skilled artisan to practice the presently claimed invention without undue experimentation. For example, the specification describes the kind of *E. coli* cells that may be employed, including the genotypes of such cells. *See Spec.* at page 14, lines 21-23. The specification also states that makes it possible to produce “a large number of oligosaccharides obtained by glycosylation of lactose.” *Spec.* at page 16, lines 15-18. The specification goes on to describe how this glycosylation can be accomplished to produce a variety of oligosaccharides. This description includes examples of specific cells, enzymes, and substrates that can be used to make different oligosaccharides. *See, e.g.*, *spec.* at page 17, line 34 – page 20, line 13. The specification also includes actual working examples demonstrating the production of oligosaccharides using the claimed method. Based on this description, one of skill in the art could readily make minor modifications to practice the full scope of the claimed method. Indeed, biosynthetic pathways and the effects of a variety of enzymes on oligosaccharide production are known in the art. “A patent need not teach, and preferably omits, what is well known in the art.” MPEP § 2164.01 (citations omitted). Thus, a skilled artisan could readily practice the claimed invention based on the guidance provided by the specification. Accordingly, the claims are enabled.

Even if the examiner persists in rejecting the claims as allegedly lacking enablement, the rejection should be withdrawn as to at least claim 7. Claim 7 specifies that the enzyme of claim 1 is one of a recited list of glycosyl-transferases. The specification describes how these specific glycosyl-transferases can be used with *E. coli* cells to produce oligosaccharides. For example, the working examples describe the use of some the recited glycosyl-transferases, as

discussed above. Because a skilled artisan could practice the claimed invention without undue experimentation using these glycosyl-transferases, at least claim 7 is enabled.

**IV. Claim Rejections – 35 U.S.C. § 103**

**A. Bettler in view of Kozumi**

Claims 1, 2, 5-14, 18-20, 26-28, and 39 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Bettler in view of Kozumi. The rejection is based on the reasons “explained in the previous Office Action.” Office Action at 9. Applicants respectfully traverse this ground of rejection.

As discussed in Applicants’ amendment of May 30, 2006, one of skill in the art would have no motivation to combine Bettler and Kozumi, much less any expectation of success, because it was known in the art that rapid uptake of sugars by lactose permease disrupts membrane function, possibly by causing collapse of the membrane potential. This phenomenon, which results in growth inhibition and eventually cell death, is known as “lactose killing.” Given this knowledge in the art, a skilled artisan would have no reason to combine the teachings of Bettler and Kozumi, much less have an expectation of success.

The Office Action states that “lactose killing as reported in the cited references is present in *E. coli* cells that have been growing on a limited supply of lactose when they are then provided with excess lactose but not in cells growing on other carbon source when supplied with lactose (see Dykhuizen et al.).” Office Action at 9-10. However, *E. coli* cells growing on carbon sources other than lactose have no reason to be killed by lactose, because their lactose permease is not induced since they have been grown in the absence of lactose. Table 2 of Dykhuizen demonstrates this point. Specifically, Table 2 shows that cultivation of *E. coli* cells on glucose or galactose in the presence of IPTG, which is an inducer of the lactose permease, results in a strong lactose killing effect. The authors conclude on page 878, column 2, lines 11-17, that “there is strong correlation between the amount of lactose permease and the amount of lactose killing.” In other words, increased amounts of lactose permease result in increased amounts of lactose killing. According to the claimed method, the cells can be grown on glucose or glycerol, and since their lactose permease is induced by

IPTG, they should be killed by lactose according to the data presented in Dykhuisen. Surprisingly, this is not the case. Thus, Bettler in view of Kozumi does not render the claimed invention obvious.

The Office Action also states that Ahmed teaches that “the amount of growth inhibition produced by lactose can be diminished by growing the cells in buffers with a pH of about 6.0, high levels of  $\text{Na}^+$  and low levels of  $\text{K}^+$  and/or by reducing the rate of import of lactose into the cell (see Ahmed et al. and Dykjuizen et al.).” Office Action at 10. However, it is not clear whether these conditions affect the lactose permease activity. A skilled artisan would thus be afraid that these conditions may inhibit the lactose internalization. In addition lowering the pH and increasing the sodium level reduces the metabolic activity of the cells. Like proteins synthesis, oligosaccharide synthesis is an energy intensive process that is best carried out in fully metabolically active cells. A skilled artisan would thus think that conditions of low pH or high sodium level are likely to reduce the productivity of the system. In fact, the claimed process has been performed at pH 6.8, and it has been observed that an accidental drop of the pH dramatically reduces the productivity of the process.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

**B. Bettler in view of Kozumi in further view of Johnson and Gotschlich**

Claim 30 stands rejected under 35 U.S.C. § 103 as allegedly obvious over Bettler in view of Kozumi in further view of Johnson and Gotschlich. Applicants respectfully traverse this ground of rejection.

Bettler in view of Kozumi do not teach or suggest the claimed invention, as discussed above, and Johnson and Gotschlich fail to remedy this deficiency. For at least this reason, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

**Conclusion**

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date December 28, 2006

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